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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,773	MICHELL ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/2/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 4/2/09 was entered.

Claims 3-8 and 23-25 are pending in the present application.

Applicants elected previously the following species: (a) subspecies *tularensis* as a species of a strain of *Francisella tularensis*; and (b) purF as a species of a gene encoding an enzyme in the purine pathway.

Upon further consideration and particularly in light of a new ground of rejection set forth below, the subspecies *novicida* of a strain of *Francisella tularensis* is rejoined with the previously elected subspecies *tularensis.* Therefore, claim 8 is rejoined for examination.

Accordingly, claims 3-8 and 23-25 are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 103(a) as being unpatentable Drabick et al. (Vaccine Research 6:67-74, 1997; IDS) in view of Karlsson et al. (Microbial & Comparative Genomics 5:25-39, 2000; IDS), Gray et al. (FEMS Microbiology Letters 215:53-56, 2002; IDS) and Gicquel et al. (US 6,261,568) was withdrawn in light of Applicant's arguments of record and in favor of the following new ground of rejection.

Claim Objections

Claim 23 is objected to because of the phrase "administering to an animal an effective amount of a live strain *Francisella* species wherein a gene that encodes an

enzyme active early in the purine pathway has been inactivated" is unclear as written. This is because in the absence of the instant specification, the term "wherein a gene" in the above phrase could refer to a gene in an animal rather than to a gene in a live strain *Franciesella* species. Therefore, the examiner suggests the following minor modification - - a live strain *Francisella* species comprising a gene that encodes.....- -.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-8 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of preventing infection *by Francisella tularensis* subspecies *novicida or Francisella tularensis LVS* in a mouse, said method comprising administering intraperitoneally to a mouse an effective amount of a live strain of *Francisella tularensis* subspecies *novicida* mutant having an inactivated purF gene, to produce a protective immune response in said mouse against *Francisella tularensis* subspecies *novicida or Francisella tularensis LVS*;

does not reasonably provide enablement for **a method of preventing infection by any other Francisella species by administering into any other animals through any other routes of delivery an effective amount of any other live strain of *Francisella* species having any other gene that encodes an enzyme active early in**

the purine pathway being inactivated as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. ***This is a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The present disclosure is not enabled for the instant broadly claimed invention for the reasons discussed below.

1. The breadth of the claims

The instant claims are directed to a method of preventing or treating infection by any *Francisella* species, the method comprising administering to any animal (e.g., humans, mice, rabbits, squirrels, muskrats, rats) by any route of delivery (e.g., oral, inhalation, intraperitoneal, intravenous or subcutaneous injection) an effective amount of any live strain of *Francisella* species (e.g., *Francisella tularensis (subspecies tularensis or type A, palaeartica or type B, mediaasiatica and palaearctica japonica), Francisella novicida and Francisella philomirgia*) as long as a gene that encodes any enzyme active early in the purine pathway (e.g. purF gene, purD gene, purN gene, pur T gene, purL

gene, purM gene and others) has been inactivated to produce a protective immune response in the animal.

2. The state and the unpredictability of the prior art

At about the effective filing date of the present application (3/27/03), the attenuated *F. tularensis* LVS vaccine whose genetic changes responsible for the attenuating phenotype are not defined or characterized at the molecular level was and still is the only effective vaccine against tularemia as evidenced at least by the teachings of Ellis et al (Clin. Micr. Review 15:631-646, 2002; IDS); Chen et al (Vaccine 21:3690-3700, 2003); Shen et al (Microbial Pathogenesis 37:107-110, 2004) and Quarry et al. (Vaccine 25:2011-2018, 2007). Additionally, Ellis et al stated "The aromatic amino acid and purine biosynthesis pathway have already been identified from genome sequence information as targets for the construction of a defined attenuated mutant (94,138). However, **the utility of this approach is limited because, as outlined in a previous section of this review, work to date has failed to devise methods for the construction of allelic replacement mutants of *F. tularensis***" (page 640, col. 2, bottom of third paragraph). In 2004, Shen et al also stated "***F. tularensis* is exceptionally difficult to manipulate genetically. This is hampering the development of rationally attenuated vaccine strains. *F. novicida* shares a lot of genetic homology with *F. tularensis* and is more amendable to genetic manipulation**" and "**wild-type *F. novicida* elicits almost no protection in mice against challenge with virulent *F. tularensis***" (see at least the abstract). Even with the effective *F. tularensis* LVS vaccine, Chen et al taught and demonstrated that **the**

degree of protective immunity conferred by vaccination with *F. tularensis* LVS vaccine against subsequent challenge varies at least with the virulence of the challenge pathogen strain, host genetic background and route of initiation of infection (see at least the abstract). Furthermore, although Karlsson et al (Microbial & Comparative genomics 5:25-39, 2000; IDS) revealed genomic sequences of the *Francisella tularensis* Strain Schu 4 containing genes that could encode all of the enzymes in the purine biosynthetic pathway and suggested that the data could be used to develop defined rationally attenuated mutants of *F. tularensis* which could be used as replacements for the existing LVS vaccine; Karlsson et al also noted that **the position in the synthetic pathway where purine synthesis is blocked has a differential influence on the level of attenuation of the pathogen and that different pathogens have different requirements for purine precursors that can limit their ability to cause disease; and therefore it would be difficult to predict which mutations might result in attenuated *F. tularensis* strains that could be suitable for live vaccine development** (see at least the abstract and page 36, last paragraph continues to second paragraph on page 37).

3. The amount of direction or guidance provided

The instant specification shows by exemplification the preparation of *Francisella tularensis* subspecies *novicida* purA mutant, and characterization of this purA mutant for growth *in vitro* and in a mouse macrophage assay in comparison *with F. novicida* CG57 (purF mutant) provided by Dr. F. Nano and the wild-type *F. novicida* U112. Additionally, Applicants showed that while *F. novicida* purA mutant (intraperitoneal inoculation)

conferred only partial protection in Balb/c mice challenged with *F. novicida* U112 (1/5 survivors) and **this response was not dose dependent** (Table 6), *F. novicida purF* mutant (intraperitoneal inoculation) could confer complete protection against a *F. novicida* challenge in Balb/c mice and this response was dose dependent (Table 7) as well as against *F. tularensis* LVS challenge in Balb/c mice (Table 8). The exemplified data is noted and considered.

However, the above evidence is not reasonably extrapolated to the instant method of preventing or treating infection by a *Francisella species* in an animal as broadly claimed. Firstly, the instant specification fails to provide sufficient guidance for a skilled artisan on how to construct any other allelic replacement mutants of *Francisella* species apart from the disclosed *Francisella tularensis* subspecies *novicida* purA mutant and purF mutant, particularly in light of the teachings of Shen et al (Microbial Pathogenesis 37:107-110, 2004) who in 2004 stated "***F. tularensis* is exceptionally difficult to manipulate genetically. This is hampering the development of rationally attenuated vaccine strains. *F. novicida* shares a lot of genetic homology with *F. tularensis* and is more amendable to genetic manipulation**" (see at least the abstract).

Secondly, the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain a prophylactic immune response in mice against a wild type *F. tularensis* subspecies *novicida* by administering an effective amount of *F. tularensis* subspecies *novicida* purF mutant through any other routes of delivery apart from the intraperitoneally administration. Quarry et al (Vaccine 25:2011-2018, 2007) taught and

demonstrated at least that **no protection was observed** with the same *F. tularensis* subspecies *novicida* purF mutant in mice following subcutaneous immunization, let alone in other animals (see at least the section 3.3 on page 2016 and Table 2). Moreover, Quarry et al also demonstrated that ***F. tularensis* subspecies *novicida* purF mutant also failed to induce a protective immune response against challenge with the virulent subspecies *tularensis* strain SchuS4** (see Table 2). Quarry et al further taught that ***F. tularensis* subspecies *novicida* purA mutant did not provide protection against a subsequent challenge with lethal doses of *F.tularensis* subspecies *novicida* or against a subspecies *tularensis* challenge in Balb/c mice**, let alone in other animals, even though **both of these purF and purA mutants were attenuated** (see at least the abstract and page 2017, col. 2, bottom of third paragraph).

Thirdly, there is no evidence in the instant specification indicating that at least *F. tularensis* subspecies *novicida* mutant with an inactivated purD, purN, purT or purM gene would confer a similar prophylactic immune response in mice as that conferred by the *F. tularensis* subspecies *novicida* purF mutant, let alone in other animals, particularly in light of the teachings of Karlsson et al which disclose that **it would be difficult to predict which mutations might result in attenuated *F. tularensis* strains that could be suitable for live vaccine development** (see at least the abstract and page 36, last paragraph continues to second paragraph on page 37). Moreover, even 4 years after the effective filing date of the present application (3/27/2003) Quarry et al stated "These findings suggest that **purine auxotrophs of *F. tularensis* should be**

further evaluated as live attenuated vaccines against tularemia, but that differential effects are seen depending on which step in the biosynthesis pathway is inactivated" (see the abstract).

Fourthly, in light of the teachings of Chen et al (Vaccine 21:3690-3700, 2003) who taught and demonstrated that **the degree of protective immunity conferred by vaccination with *F. tularensis* LVS vaccine against subsequent challenge varies at least by various factors such as the virulence of the challenge pathogen strain, host genetic background and route of initiation of infection**, coupled with the lack of sufficient guidance provided by the present application it would have required undue experimentation for a skilled artisan to make and use a method of preventing or treating infection by a *Francisella* species in an animal as broadly claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the state and the unpredictability of the tularaemia vaccine art, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633